Association of Retinal Age Gap and Risk of Kidney Failure: A UK Biobank Study

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Association of Retinal Age Gap and Risk of Kidney Failure

### Design

Prospective cohort study

N = 35,864 participants in UK Biobank Study with retinal images and no ESKD

Median follow-up: 11 years

### Exposure

**Retinal age gap**

= Model-based retinal age minus Chronological age

**Analysis:** Deep learning prediction model used to characterize retinal age

### Findings

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal age gap, per 1-year greater</td>
<td>1.10 (1.03-1.17)</td>
</tr>
</tbody>
</table>

**Quartiles of retinal age gap**

- **Q1**
  - REF

- **Q2**
  - 1.03 (0.54-1.99) | 0.9

- **Q3**
  - 2.04 (1.07-3.91) | 0.03

- **Q4**
  - 2.77 (1.29-5.93) | 0.009

### CONCLUSION:

Retinal age gap was significantly associated with incident ESKD and may be a promising non-invasive biomarker of incident ESKD.
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Abstract

**Rationale & Objective:** The incidence of end stage kidney disease (ESKD) is known to increase with age. We have previously developed and validated retinal age based on fundus images used as a biomarker of ageing. However, the association of retinal age with ESKD is not clear. We investigated the association of the difference between retinal age and chronological age, the retinal age gap, and the future risk of ESKD.

**Study design:** Prospective cohort study.

**Setting & participants:** 11,052 UK Biobank study participants without any reported disease for characterizing retinal age in a deep learning algorithm. 35,864 other participants with retinal images and no ESKD were followed to assess the association between retinal age gap and the risk of ESKD.

**Exposure:** Retinal age gap defined as the difference between model-based retinal age and chronological age.

**Outcome:** Incident ESKD.

**Analytical approach:** A deep learning prediction model used to characterize retinal age based on retinal images and chronological age. Cox proportional hazards regression models to investigate the association of retinal age gap with incident ESKD.

**Results:** After a median follow-up of 11 years (interquartile range [IQR]: 10·89-11·14), 115 (0·32%) participants were diagnosed with ESKD. Each one-year increase in retinal age gap was independently associated with a 10% increase in the risk of incident ESKD (hazard ratio [HR] = 1·10, 95% confidence interval [CI]: 1·03-1·17, P = 0·003). Participants with retinal age gaps in the fourth quartile had a significantly higher risk of incident ESKD compared to those in the first quartile (HR = 2·77, 95% CI: 1·29-5·93, P = 0·009).

**Limitations:** Limited generalizability because of the composition of participants in the UK Biobank study.

**Conclusion:** Retinal age gap was significantly associated with incident ESKD and may be a promising non-invasive biomarker for of incident ESKD.

**Keywords:** retinal age, biomarker, kidney, end stage kidney disease, ageing
Plain Language Summary

There is a pressing need to identify early predictive biomarkers of ESKD, given its associated substantial morbidity and mortality. Ageing biomarkers have been associated with ESKD but their clinical application has been challenging. This study identified retinal age gap (retina-predicted age minus chronological age), a clinically validated and artificial intelligence powered ageing biomarker based on retinal imaging, was associated with the future risk of ESKD among UK residents. This non-invasive and ageing biomarker may hold promise to assist in the identification of people at elevated risk for ESKD.
Introduction
At an advanced stage of chronic kidney disease (CKD), end stage kidney disease (ESKD) is characterized by severely decreased kidney function. ESKD with its associated complications places a large burden both on individuals and the health care system.[1 2] Globally, 697.5 million cases of all-stage CKD were recorded in 2017.[2] The prevalence of CKD and ESKD rises dramatically with age,[3 4] and in light of the unprecedented growth rate of the world’s aging population, the total burden of disease is expected to continue increasing well into the future.[3 5 6]

Although greater chronological age is correlated with increased morbidity, significant heterogeneity exists in the health of individuals with the same chronological age.[7] Similarly, the rate of age-related renal damage in individuals of the same chronological age and seemingly comparable clinical profiles exhibit significant variation.[8] A more accurate indicator of age-related morbidity and mortality is the biological age, which is a measure of the body’s functional capability.[9] With growing evidence showing the relationship between ageing biomarkers and CKD or ESKD[7-9], the significance of quantifying the biological age in renal disease lies in its diagnostic and prognostic potential, enabling early detection and individualization of interventions in the management and prevention of ESKD. However, current investigations into the clinical value of existing ageing biomarkers for ESKD may be limited due to several drawbacks in the study designs, including the cross-sectional designs and small sample sizes.[10] Moreover, the invasive feature of obtaining molecular aging markers and the costly, time-consuming nature of imaging phenotypic aging biomarkers have excluded them from being used in large-scale monitoring of the impacts of the ageing process on CKD or ESKD.

The retina has long been considered as a window to the kidney, as common microvascular structures, physiological pathways and pathogenic pathways are shared between the two organs, inextricably linking them in many diseases.[11 12] Consistent evidence has demonstrated the strong association of retinal microvascular changes, including venular dilatation and arteriolar narrowing with ESKD.[13-17], which opens the door for retinal imaging, as a fast, safe, non-invasive and cost-effective method, to supplement CKD screening. With the advent of deep
learning (DL) systems in the interpretation of retinal photographs, promising results have been shown in studies regarding the utility of retinal images in predicting kidney functions via the DL techniques.[13 17]

Our research group has developed and validated a deep learning system that accurately predicts chronological age in healthy population based on fundus images. Furthermore, we have identified the retinal age gap, defined as the gap between retina-predicted age and chronological age, to be a new, non-invasive, fast and accurate marker of biological aging, predictive for mortality and neurodegenerative diseases such as Parkinson’s disease in previous studies.[18 19] With retinal age gap being a strong reflection of the biological aging process, there is potential for it to be a biomarker to identify patients at high risk of ESKD, alongside other retinal changes correlated to kidney disease. Therefore, in this study, we aimed to explore the association between the retinal age gap and the future risk of incident ESKD using the prospective cohort of the UK Biobank study.

Methods

Study population
The UK Biobank is a large population-based prospective cohort study of over 500,000 UK residents aged 40 to 69 years. Participants were recruited between 2006-2010 and registered in the National Health Service (NHS). At baseline, participants completed electronic questionnaires on socio-demographics, lifestyle, environmental exposures, medical history, cognitive functions and underwent physical and functional examinations as well as comprehensive ophthalmic examinations, including retinal photographs. Biological samples including blood, urine, and saliva were also collected. More details about UKB biobank are available elsewhere.[20]

The study was reviewed and approved by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee (11/NW/0382) and data used in the present study was accessed through the Biobank consortium (Application No: 62489). Since this is a publicly identified dataset, the Guangdong Provincial People's Medical
Research Ethics Committee waived the requirement for ethics approval. The study was in accordance with the Helsinki declaration with informed consent from all participants.

**Fundus photography**
Paired retinal fundus and optical coherence tomography imaging were conducted in 2010 using OCT, Topcon 3D OCT 1000 Mk2, Topcon Corp, Tokyo, Japan. A 45-degree non-mydriatic and non-stereo retinal fundus imaging centred on the optic disc and macular were captured for each eye. In total, 131,238 fundus images were collected from 66,500 participants at baseline from the UK Biobank study, but only 80,169 images from 46,969 participants met image quality criteria for inclusion. Details of the image quality check can be found elsewhere.[21]

**Deep learning model for age prediction**
A total of 80,169 images from 46,969 participants met the image quality criteria and were included in the analysis. Consistent with the methods used in previous studies for age prediction,[7 22 23] 19,200 fundus images from 11,052 participants without any reported previous disease at baseline were used to build a deep learning (DL) model for age prediction. Each participant had one fundus image for each eye. To maximize data pool for training and validation, images from both eyes (if available) were used. Out of the remaining 35,917 participants, fundus images from 35,864 of these participants without a history of ESKD at baseline (date of fundus image acquisition) were used to investigate the relationship between retinal age gap and incident ESKD. For the 35,864 participants, the right eye images from 31,991 participants and left eye images from those without available right eye images (N=3873) were used to calculate the retinal age gap.

Details on the development and validation of the DL model are presented elsewhere.[19] The accuracy of the DL prediction model was assessed by mean absolute error (MAE) and correlation between predicted retinal age and chronological age. The MAE is a widely used indicator to evaluate the accuracy of ageing biomarkers, which is determined as the mean absolute value of the difference between the predicted age and the ground truth (i.e., chronological age in our study). A smaller MAE indicates a higher accuracy of the ageing biomarker.[24-27] The DL model was able
to accurately predict retinal age with a correlation coefficient of 0.81 (P < 0.001) between retinal age and chronological age and an overall mean absolute error (MAE) of 3.55 years.

**Retinal age gap definition**
Retinal age gap was defined as the difference between the retinal age predicted by the DL model based on fundus images and the chronological age. A positive value of retinal age gap suggested an “older” appearing retina while a negative value suggested a “younger” appearing retina.

**End stage kidney disease ascertainment**
ESKD status and date of diagnosis were ascertained via data linkage to the National Health Service (NHS) Digital for participants in England, Scotland and Wales, national death register data. ESKD was defined by ICD-10 (International Classification of Diseases, Version 10) codes and OPCS4 (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures - Version 4) codes according to the algorithm devised by UK Biobank. (Supplement S1) The follow-up period was defined as the time between baseline (date of fundus image acquisition) to the first occurrence of ESKD or lost to follow-up or death, whichever came the earliest.

**Covariates**
Factors associated with ESKD[28] were included as confounding factors in our analyses. These factors included age, gender, ethnicity (classified as white/non-white), Townsend deprivation indices [TDI]; lifestyle factors including smoking status (classified as current/previous or never), alcohol drinking status (classified as current/previous or never), physical activity level (classified as an above physical recommendation or not), general health status (classified as excellent/good and fair/poor), history of diabetes mellitus (DM), systolic blood pressure, body mass index, serum levels of cholesterol and estimated glomerular filtration rate (eGFR). TDI was used as a proxy measure of socioeconomic status based on the area postcode. Physical activity was assessed using self-reported questionnaires from the validated short International Physical Activity Questionnaire (IPAQ). The intensity of physical activity was classified as meeting recommendation or not according to the criteria whether a person met the UK physical activity guidelines of 150 minutes.
of walking or moderate activity per week or 75 minutes of vigorous activity.[29 30] General health status was derived from self-reported touchscreen questionnaires (excellent, good, fair and poor). Participants with any records of self-reported or doctor-diagnosed DM, a usage of anti-hyperglycaemic medication or insulin treatment or a HbA1C ≥48mmol/mol were considered to have a diagnosis of DM. The estimated glomerular filtration rate (eGFR) was calculated with CKD-Epidemiology Collaboration (CKD-EPI) equation.[31]

**Statistical analyses**

Continuous variables of the baseline characteristics of all participants were described through mean/standard deviation (SD) or median/interquartile range (IQR), while categorical variables were presented as numbers/percentages. Comparisons between the continuous and categorical variables at baseline were performed by unpaired t-tests and Chi-square tests, respectively. Two Cox proportional hazards regression models were fitted to explore the relationships between the incidence of ESKD and the retinal age gap, first with retinal age gap expressed as a continuous linear term and then as quartiles. All variables were assessed for the proportional hazards assumption before they were fitted into Cox proportional hazards regression models. In Cox regression models, we adjusted for covariates, with Model I being adjusted for baseline age, gender, and ethnicity and Model II being adjusted for all covariates in Model I plus additional covariates including TDI, smoking status, drinking status, physical activity level, diabetes mellitus, systolic blood pressure, body mass index (BMI), cholesterol, eGFR and general health status. We also performed a trending test to investigate if there was an increasing association treading across different quartiles of retinal age gaps with incident ESKD. Besides, subgroup analyses stratified by sex were further conducted.

To validate the results, several sensitivity analyses were performed. To investigate the potential non-linear associations between retinal age gap and incident ESKD, we performed sensitivity analyses further adjusted for age-squared in addition to all the co-variates in Model I and Model II. Further, restricted cubic spline analysis was also fitted to investigate the non-linear relationship between retinal age gap and incident ESKD. We also investigated whether retinal age acceleration residual (calculated as the residual resulting from regressing retinal age on chronological age)
[32] was associated with ESKD. To account for major comorbidities, Charlson Comorbidity index (CCI) scores were incorporated into the model. [33] As a major risk factor for ESKD, albuminuria was further incorporated in the model as sensitivity analysis. To consider the competing risk of death on incident ESKD, we performed the competing risk analysis using Fine and Gray model to examine the association between retinal age gap with ESKD risks competing to mortality.

A two-sided p value of < 0.05 was considered statistically significant. All statistical analyses were performed using R (version 3.3.0, R Foundation for Statistical Computing, www.R-project.org, Vienna, Austria) and Stata (version 13, StataCorp, Texas, USA)

Results
Study sample
Baseline characteristics of 35,864 participants without any ESKD history at baseline are shown in Table 1. Participants had a mean age of 56.75 ± 8.04 years and 55.7% were female. There were significant differences across retinal age gap quartiles in all covariates (All P < 0.05) except for history of DM. The distribution of retinal age gap and retinal age residual were showed in Supplement figure S1-2. The ranges for each quartile of retinal age gaps were: Q1 (range: -27.91 to -4.18 years), Q2 (range: -4.18 to -1.18 years), Q3 (range: -1.18 to 1.79 years), Q4 (range: 1.79 to 19.04 years).

Incident ESKD
After a median follow-up of 11 years (interquartile range [IQR]: 10.89-11.14, range: 0.02-11.39), a total of 115 (0.32%) participants were diagnosed with ESKD while 1087 participants (3.0%) died from all causes. As shown in Supplement Table S1, compared to the non-ESKD group, participants diagnosed with ESKD tended to be older, male, white ethnicity, smokers, alcohol consumers, with higher TDI, BMI and increased circulating levels of cholesterol, in addition to a history of DM and hypertension, and with worse general health status.

Retinal age gap and incident ESKD
After adjusting for age, gender and ethnicity in Model I, each one-year increase in the retinal age gap was independently associated with a 9% increase in the risk of incident ESKD (Model I: Hazard Ratio [HR] = 1.09, 95% confidence interval [CI]: 1.03-1.15, P = 0.001), as shown in Table 2. This association remained significant after further adjustments (Model II: HR = 1.10, 95% CI: 1.03-1.17, P = 0.003, Table 2).

After adjusting for age, gender and ethnicity, participants with retinal age gaps in the fourth quartile had a significantly higher risk of incident ESKD compared to those in the first quartile (HR = 2.75, 95% CI: 1.44-5.25, P = 0.002). The association remained significant in Model II with further adjustments (HR = 2.77, 95% CI: 1.29-5.93, P = 0.009, Table 2). A trend of increasing association was noted with incident ESKD across different quartiles of retinal age gaps (P = 0.004). Supplement Table S2 further displays the associations between various variables and incident ESKD using the multivariable Cox regression model.

Sensitivity analysis
Similar results were noted with CCI scores incorporated into the model as shown in Supplement table S3. After further including albuminuria in the fully adjusted model, the association between retinal age gap and incident ESKD remained significant (HR = 2.65, 95% CI: 1.01-6.91, P = 0.047, Supplement table S4). With age-squared adjusted for in the Cox regression models, the association of retinal age gap with ESKD remained robust (Model II: HR = 2.83, 95% CI: 1.29-6.23, P = 0.01, Supplement Table S5). Restricted cubic spline model showed non-significant non-linear relationship between retinal age gap and incident ESKD (P_{non-linear} = 0.788, Supplement Figure S3). Participants with higher quartiles of retinal age gaps showed a higher risk of ESKD events. In addition, the retinal age acceleration residual was also significantly associated with incident ESKD (Supplement Table S6). In the competing risk analysis, similar significant results were observed (Supplemental Table S7).

Subgroup analysis
In the fully adjusted models, we found that each one-year increase in the retinal age gap was independently associated with an 8% and 13% increase in the risk of incident ESKD in male and
female, respectively (HR = 1.08, 95% CI: 1.00-1.17, P = 0.04; HR = 1.13, 95% CI: 1.02-1.27, P = 0.02) and participants with retinal age gaps in the fourth quartile had a higher risk of incident ESKD compared to those in the first quartile in female (HR = 4.73, 95% CI: 1.16-19.23, P = 0.03) and in male (HR = 2.23, 95% CI: 0.91-5.91, P=0.08), respectively (Supplemental Table S8).

Discussion
In this prospective large-scale population-based study, we demonstrated that each year increase in retinal age gap was independently associated with a 10% increase in the risk of incident ESKD. The risk of developing ESKD in participants with retinal age gaps in the fourth quartile was 2.77-fold higher than those in the lowest quartile. These findings suggested retinal age gap is a promising biomarker of future occurrence of ESKD independent of traditional risk factors.

This study demonstrates the association of retinal age gap as a biological aging biomarker with future ESKD incidence. A growing number of studies have investigated the association of ageing biomarkers with CKD and ESKD. For example, a Mendelian randomization study showed that polygenetic risk of telomere attrition was significantly associated with a higher risk of kidney function decline.[34] DNA methylation, a well-established aging biomarker, was associated with lower renal function, but conflicting results surround this association.[10 28] Regardless, retinal age is a promising biomarker for future ESKD risks, possessing many advantages over most of these existing ageing biomarkers including its non-invasive nature, ease of calculation and accuracy.

Several mechanisms might explain the association between the retinal age gap and incident ESKD. Firstly, the connection between the retina and kidneys is supported by the common developmental pathways of the retina and kidney, with the organs sharing similarities in structural characteristics.[11 35 36] Common pathophysiological mechanisms such as renin-angiotensin system dysfunction,[37-39] inflammation,[40 41] endothelial dysfunction,[42] and oxidative stress underlie disease development and progression in both retinal and renal disease[43] when the organs are exposed to risk factors such as smoking, DM, hypertension, hypercholesterolemia.[35 36 44] Consistent with this finding, numerous studies have indicated that retinal vessel alterations
(e.g. venular tortuosity, arteriolar narrowing, retinal vascular caliber and geometry) were associated with declined renal function and a future risk of CKD. This association is bidirectional as it has also been demonstrated that patients with CKD and ESKD patients are at a higher risk of developing retinal disorders. Since many of the above shared pathophysiological mechanisms mediate age-related changes in the retina and kidney, ageing of the retina is comparable to ageing of the kidneys, resulting in abnormalities including basement membrane thickening, decreased density of microvessels and decreased arteriole-venule ratio that precipitate renal and retinal disease.

Therefore, as a clinical parameter, the retinal age gap is significantly associated with higher future risk of ESKD and presents itself as a competitive and promising proxy related with ESKD. The low early diagnosis rate of ESKD in combination with the high morbidity and mortality associated with delayed intervention make it imperative to identify individuals at a high risk of ESKD. With the introduction of AI technology, fundus images could be used to reflect renal dysfunction and risk of CKD. The non-invasive, cost-effective and accessible nature of DL-assisted retinal imaging presents opportunities of large-scale screening of CKD/ESKD, thus allowing for the early transferal to renal specialists and personalized interventions if necessary. Furthermore, retinal imaging is highly amendable to repeated and longitudinal assessments, facilitating long-term monitoring for CKD, which, coupled with the potential of retinal age being a predictor of mortality, could help clinicians to estimate the rate and path of progression of CKD/ESKD more accurately.

Our findings revealed that retinal age gap was a promising biomarker for future risk of ESKD. Previous studies have verified retinal age gap as a biomarker for vascular stiffness and vascular ageing. Retinal age gap may provide an integrated measurement of vascular ageing which reflects the high-dimensional morphometric patterns in the microvasculature deviated from normal ageing. The association of retinal age gap with incident ESKD could be interpreted as a byproduct of accelerated vascular ageing in kidney. The non-invasive, fast and cost-effective features of retinal imaging enable the utility of retinal age gap as a screening and triage tool for ESKD, thus potentially improving the current low compliance rate to kidney disease screening.
Apart from the large sample size and the prospective study design, our study had a number of strengths including comprehensive adjustments for confounding factors and standardized protocol in the acquisition of fundus images. However, there are several limitations of this study. Firstly, the selection bias of the UK Biobank cohort cannot be overlooked as it mainly consisted of white ethnicity, relatively healthy, young and well-educated participants compared to the general population, which might limit the generalizability of the results. Secondly, further subgroup analysis was limited due to the limited number of patients with incident ESKD, and a lack of longitudinal data of fundus images precluded us from exploring the association of dynamic changes of retinal age gap with incident ESKD. Lastly, the possibility of residual confounding cannot be fully excluded.

In conclusion, retinal age gap, a biological ageing marker, was significantly associated with incident ESKD and may have potential to contribute to identification of people at elevated risk for ESKD. Future studies are needed to investigate the association of dynamic changes of retinal age gap with incident ESKD to evaluate the predictive value of retinal age gap in assessing the risk of ESKD.

**Supplementary Material:**

Figure S1. Distribution of retinal age gap (based on right eyes).

Figure S2. Distribution of retinal age acceleration residual (based on right eyes).

Figure S3. Association between retina age gap and incident ESKD risk, allowing for non-linear effects.

Item S1. Definition of end stage kidney disease.

Table S1. Baseline characteristics of study participants stratified by incident ESKD.

Table S2. Association of variables and incident ESKD using multivariable cox regression model.

Table S3. Association between retinal age gap with incident ESKD adjusting for CCI.

Table S4. Association between retinal age gap with incident ESKD further adjusting for albuminuria.
Table S5. Association between retinal age gap with incident ESKD further adjusting for age-squared.
Table S6. Association between retinal age acceleration residual with incident ESKD.
Table S7. Association between retinal age gap with incident ESKD using competing risk model.
Table S8. Association between retinal age gap with incident ESKD stratified by gender.

**Article Information**

*Authors’ Contributions:* Study concept and design: ZZ, WW, MH, XY; acquisition, analysis, or interpretation: All authors; Statistical analysis: ZZ, SZ; Obtained funding: MH, XY, ZZ; Administrative, technical, or material support: ZZ, WW, MH, XY; Study supervision: MH, XY.

Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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12. Elias MF, Torres RV, Davey A. The Eye is the Window to the Kidney and Brain. EBioMedicine 2016;5:24-5 doi: 10.1016/j.ebiom.2016.02.010[published Online First: Epub Date]].


Table 1. Baseline Characteristics of the Study Participants and Stratified by Quantiles of Retinal Age Gap.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Total</th>
<th>Retinal Age Gap</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>N</td>
<td>35864</td>
<td>8966</td>
<td>8966</td>
</tr>
<tr>
<td>Age, mean (SD), yrs</td>
<td>56.75</td>
<td>63.1 (4.80)</td>
<td>59.3 (6.43)</td>
</tr>
<tr>
<td>Age group, mean (SD), yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤55 years</td>
<td>1.68</td>
<td>-5.68</td>
<td>-2.44</td>
</tr>
<tr>
<td></td>
<td>(1.26)</td>
<td>(0.84)</td>
<td></td>
</tr>
<tr>
<td>&gt;55 years</td>
<td>-3.36</td>
<td>-7.52</td>
<td>-2.70</td>
</tr>
<tr>
<td></td>
<td>(4.37)</td>
<td>(3.53)</td>
<td>(0.86)</td>
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<tr>
<td>Gender, No. (%)</td>
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</tr>
<tr>
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<td>(55.4)</td>
<td>(54.5)</td>
<td>(54.4)</td>
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<td>(44.6)</td>
<td>(45.5)</td>
<td>(45.6)</td>
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<tr>
<td></td>
<td>Never</td>
<td>Former/current</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>years</td>
</tr>
<tr>
<td></td>
<td>1582</td>
<td>442 (4.90)</td>
<td>357 (4.00)</td>
</tr>
<tr>
<td></td>
<td>(4.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting PA recommendation, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5289</td>
<td>1126</td>
<td>1271</td>
</tr>
<tr>
<td></td>
<td>(18.0)</td>
<td>(15.6)</td>
<td>(17.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>24052</td>
<td>6089</td>
<td>6029</td>
</tr>
<tr>
<td></td>
<td>(82.0)</td>
<td>(84.4)</td>
<td>(82.6)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>27.6 (4.87)</td>
<td>27.5 (4.48)</td>
<td>27.6 (4.74)</td>
</tr>
<tr>
<td>Cholesterol, mean (SD), mmol/L</td>
<td>5.66 (1.14)</td>
<td>5.65 (1.19)</td>
<td>5.71 (1.15)</td>
</tr>
<tr>
<td>eGFR, mean (SD), mL/min</td>
<td>90.2 (13.4)</td>
<td>85.0 (12.4)</td>
<td>88.0 (12.8)</td>
</tr>
<tr>
<td>History of diabetes, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>33526</td>
<td>8388</td>
<td>8378</td>
</tr>
<tr>
<td></td>
<td>(93.5)</td>
<td>(93.6)</td>
<td>(93.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>2338</td>
<td>578 (6.40)</td>
<td>588 (6.60)</td>
</tr>
<tr>
<td></td>
<td>(6.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mean (SD), mmHg</td>
<td>137.6</td>
<td>142.2</td>
<td>139.5</td>
</tr>
<tr>
<td></td>
<td>(18.5)</td>
<td>(18.5)</td>
<td>(18.7)</td>
</tr>
<tr>
<td>General health status, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent/good</td>
<td>24803</td>
<td>6460</td>
<td>6300</td>
</tr>
<tr>
<td></td>
<td>(69.6)</td>
<td>(72.3)</td>
<td>(70.5)</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>10861</td>
<td>2469</td>
<td>2635</td>
</tr>
<tr>
<td></td>
<td>(30.4)</td>
<td>(27.7)</td>
<td>(29.5)</td>
</tr>
</tbody>
</table>

SD = standard deviation; PA = physical activity; BMI = body mass index; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; Q = quartile.
<table>
<thead>
<tr>
<th>Retinal age gap</th>
<th>Model I</th>
<th></th>
<th>Model II</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal age gap, per one age (yrs)</td>
<td>1.09 (1.03, 1.15)</td>
<td>0.001</td>
<td>1.10 (1.03, 1.17)</td>
<td>0.003</td>
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<td>Retinal age gap</td>
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<tr>
<td>Q1</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
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<tr>
<td>Q2</td>
<td>1.13 (0.67, 1.90)</td>
<td>0.7</td>
<td>1.03 (0.54, 1.99)</td>
<td>0.9</td>
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<tr>
<td>Q3</td>
<td>2.04 (1.20, 3.47)</td>
<td>0.009</td>
<td>2.04 (1.07, 3.91)</td>
<td>0.03</td>
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<tr>
<td>Q4</td>
<td>2.75 (1.44, 5.25)</td>
<td>0.002</td>
<td>2.77 (1.29, 5.93)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

ESKD = end stage kidney disease; Q = quartile; HR = hazard ratio; CI = confidence interval.

Model I adjusted for age, gender, and ethnicity.

Model II adjusted for covariates in Model I + deprivation, smoking status, drinking status, physical activity, diabetes mellitus, systolic blood pressure, body mass index, cholesterol, estimated glomerular filtration rate and general health status.